Phosphorus-Substituted Azulenes Accessed *via* Direct Hafner Reaction of a Phosphino Cyclopentadienide

Anthony P. Gee[a]
Samuel D. Cosham[a]
Andrew L. Johnson[a]
Simon E. Lewis*[a]

[a] Department of Chemistry, University of Bath, Bath, BA2 7AY, United Kingdom.

S.E.Lewis@bath.ac.uk

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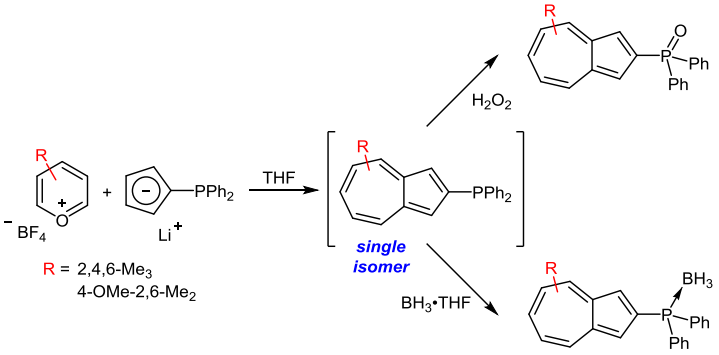

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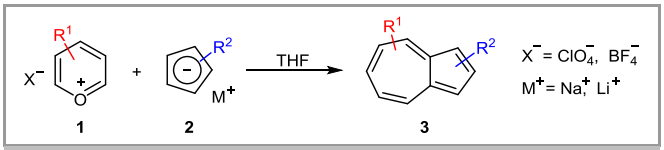
Abstract The Hafner azulene synthesis may be applied to the direct synthesis of phosphorus-substituted azulenes, when a phosphinocyclopentadienide is used as one of the reactants. The azulenyl phosphines produced in this fashion are preferentially isolated as the corresponding phosphine oxides or phosphine borane adducts.

Key words azulene, phosphine, pyrylium salt, cyclopentadienide, borane adduct

The non-alternant aromatic hydrocarbon azulene has markedly different properties from its isomer naphthalene, such as a high dipole moment and an intense blue colour.[1] In recent years, azulene motifs have increasingly been exploited in optoelectronic applications,[2] in stimuli-responsive systems[3] and in drug discovery.[4] As such, there is a continuing need for synthetic methods for accessing substituted azulenes.

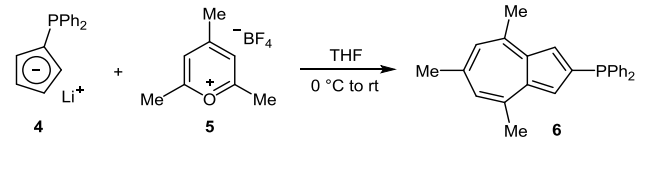
Many approaches have been reported for introducing substituents onto a preexisting azulene skeleton, such as cross-coupling,[5] C-H activation,[6] metallation,[7] and S_EAr reactions.[8] A fundamentally different approach is to employ reactions that directly form substituted azulenes from non-azulene precursors; many such reactions are known. For example, Nozoe azulene syntheses allow direct access to azulenes substituted on the five-membered ring.[9] Complementary syntheses that can give azulenes substituted on the seven-membered ring are also known,[10] of which the oldest is the Ziegler–Hafner synthesis.[11] In one variant, reported by Hafner,[11c] a cyclopentadienide anion is added to a pyrylium salt to give the desired substituted azulene (Scheme 1).



Scheme 1 Hafner's synthesis of substituted azulenes from a pyrylium salt and a metallated Cp.

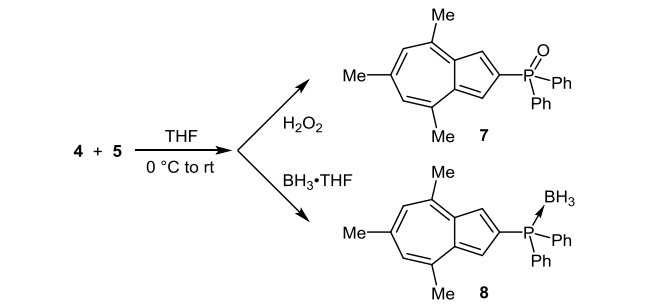
In the above transformation, substitution on the pyrylium fragment has been extensively explored (R^1 = multiple alkyl, aryl and heteroatom substituents). In contrast, the literature is notably lacking in examples of the use of substituted cyclopentadienides (i.e. $R^2 \neq H$) to access directly an azulene substituted on the 5-membered ring using the Hafner process. While Hafner has reported using sodium methylcyclopentadienide (R^2 = Me),[11c] Hansen *et al.* and Koenig *et al.* have independently described R^2 = COOMe,[12] and R^2 = COOEt[13] substituted cyclopentadienide systems, respectively. It is probable that the use of substituted Cp species in the Hafner azulene synthesis is rare because it is possible for regioisomeric mixtures of products to form (with the R^2 substituent at the azulene 1- or 2-position), which can be difficult to separate.[14] As part of an ongoing effort to synthesise azulenes bearing phosphorus substituents, we sought to establish the viability of accessing directly an azulene bearing a *P*-substituent on the 5-membered ring via a Hafner reaction employing a *P*-substituted cyclopentadienide. Azulenyl phosphines are potentially of interest as bulky monodentate ligands for transition metal catalysis.[15] The results of our studies are disclosed here.

Lithium (diphenylphosphino)cyclopentadienide **4** has been reported previously, and was synthesized by Erker's procedure.[16] When pyrylium salt **5** was treated with two equivalents of **4** in THF, 2-azulenyl phosphine **6** was formed *as the only isomer* (Scheme 2).



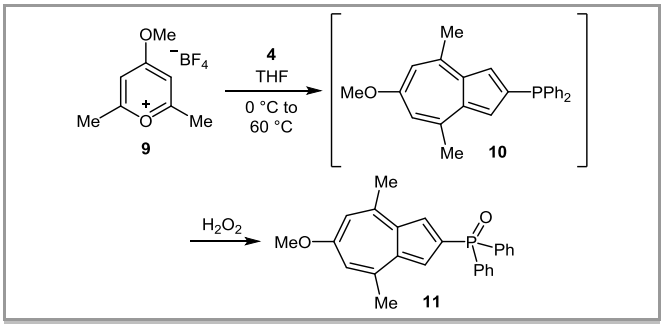
Scheme 2 Synthesis of an azulenyl phosphine by the Hafner method

To our knowledge, this is the first example of the direct synthesis of a *P*-substituted azulene by the Hafner method. The noteworthy regioselectivity of this reaction may be due to the steric bulk of the substituent on the cyclopentadienide (which is an ambident nucleophile). Since the first step in the Hafner reaction is attack of the cyclopentadienide at the pyrylium 2-position (which itself bears a methyl substituent), we envisage that attack by a cyclopentadienide carbon distal to the diphenylphosphino group will be appreciably less sterically hindered; this would lead to formation of **6**. Novel phosphine **6** was obtained in only a 3% yield; we ascribe this low yield partly to its apparent tendency to undergo aerobic oxidation to the phosphine oxide very readily (which also complicated the characterization of **6**) and partly to the co-elution of **6** and protonated **4** on silica. Variation of the reaction conditions did not lead to an improved yield, so we instead sought to effect deliberately the oxidation of **6** after its formation (with hydrogen peroxide) and isolate **7**. Such a procedure did indeed furnish **7** but in a similarly low yield (<2%). Much more successful, however, was the trapping of **6** *in situ* by formation of the corresponding phosphine-borane adduct **8** (Scheme 3). This was isolated in 12% yield in a 2 step, one-pot process.[17] As **8** was the only isomer isolated, this yield in fact compares favourably with that reported by Koenig for the synthesis of **3** (R^2 = 2-COOEt).[13] Furthermore, azulenyl phosphine-boranes are previously unknown in the literature, and our telescoped route to **8** requires only 2 steps (3 reactions) from commercial materials.



Scheme 3 Synthesis of the first azulenyl phosphine-borane.

We also explored the applicability of this "phosphino-Hafner" process to a different pyrylium salt, 4-methoxy-2,6-dimethylpyrylium tetrafluoroborate **9**.[18] Reaction of **4** with **9** required more forcing conditions than for the reaction of **4** with **5**, presumably because the methoxy substituent in **9** attenuates its electrophilicity. Analogously with **6**, the azulene **10** formed from **9** was found to be susceptible to air oxidation, so phosphine protection was once again employed. Phosphine oxide **11** could be isolated in pure form, (Scheme 4, 2% yield), but the borane adduct of **10**, although it formed in a yield comparable to that of **8**, could not be isolated in pure form.



Scheme 4 Use of an alternative pyrylium salt.

In conclusion, we have demonstrated for the first time the applicability of the Hafner azulene synthesis to the production of *P*-substituted azulenes. Novel azulenes so produced can be expected to find applications in diverse areas of research.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(14) Trends and exceptions are known. It is reported that 2,4,6,8-tetramethyl azulene may be formed selectively from **5** and **2** (R^2 = Me); in contrast it is reported that if a Zincke aldehyde is used in place of a pyrylium salt, the 1-aubsituted azulene is favoured. See reference 11c. Also of note, When R^2 = COOMe, the product with R^2 at the azulene 2-position may be formed exclusively *if MeOH is used as solvent*; see reference 12a.

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(17) *Procedure for preparation of **8**:* At 0 °C, to a suspension of 2,4,6-trimethylpyrylium tetrafluoroborate **5** (1.10 g, 5.23 mmol, 1.00 eq.) in THF (30 mL) was added a solution of lithium (diphenylphosphino)cyclopentadienide **4** (2.68 g, 10.5 mmol, 2.00 eq.) in THF (30 mL). After stirring at 0 °C for 1 h, the mixture was filtered through a pad of neutral alumina under atmosphere of argon. To the stirred filtrate, at r.t., was slowly added a solution of borane-THF complex (11.0 mL, 1.0 M in THF, 2.10 eq.). After stirring for 16 h, the reaction was quenched by the addition of methanol (10 mL). The solution was then concentrated under reduced pressure to a small volume, and added to ethyl acetate (60 mL). The solution was washed with water (3 × 50 mL) and with saturated brine, and the organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (0→10% EtOAc in petroleum ether) to give boranyldiphenyl(4,6,8-trimethylazulen-2-yl)phosphine **8** (228 mg, 0.621 mmol, 12%) as a purple solid (m.p. 148-150 °C); R_f 0.53 (3:1 petroleum ether/EtOAc); δH (300 MHz, $CDCl_3$) 7.73-7.66 (4H, m), 7.51-7.41 (6H, m), 7.46 (2H, d, $^3J_{PH}$ 5.1 Hz), 7.12 (2H, s), 2.83 (6H, s), 2.65 (3H, s), 1.44 (3H, br d); δC (75 MHz, $CDCl_3$) 149.7, 148.7, 136.5 (d, $^3J_{CP}$ 11.5 Hz), 133.0 (d, $^2J_{CP}$ 9.9 Hz), 131.1 (d, $^1J_{CP}$ 62.7 Hz), 130.8 (d, $^4J_{CP}$ 2.5 Hz), 130.6 (d, $^1J_{CP}$ 58.9 Hz), 128.5 (d, $^3J_{CP}$ 10.2 Hz), 128.3 (d, $^5J_{CP}$ 1.2 Hz), 120.8 (d, $^2J_{CP}$ 10.5 Hz), 29.0, 25.2; δP (122 MHz, $CDCl_3$) 12.38-11.65 (m); δB (96 MHz, $CDCl_3$) -34.5; ν_{max} (film) 3675, 2987, 2971, 2901, 2380 (ν_{BH}), 1578, 1537, 1483, 1468, 1435, 1408, 1394, 1377, 1333, 1290, 1218, 1187, 1140, 1102, 1027, 1066, 907, 882, 847, 809, 797, 766, 740, 690 cm^{-1}; HRMS (ESI+) m/z calc for $[C_{25}H_{26}BP + Na]^+$, 391.1763; found, 391.1796. *See ESI for complete NMR assignments.*

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